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Prenatal and postnatal exposures to endocrine disrupting chemicals and timing of pubertal onset in girls and boys: a systematic review and meta-analysis

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BACKGROUND: Globally, the ages at pubertal onset for girls and boys have been decreasing during recent decades, partly attributed to excess body fat accumulation. However, a growing body of literature has recognized that endocrine disrupting chemicals (EDCs) may play an important role in this global trend, but the association has not yet been fully established.

OBJECTIVE AND RATIONALE: EDCs can interfere with normal hormone function and metabolism and play a role in pubertal onset. We aimed to systematically identify and evaluate the current evidence on the timing of pubertal onset in girls and boys following prenatal or postnatal exposures to xenobiotic EDCs.

SEARCH METHODS: Following PRISMA guidelines, we performed a systematic literature search of original peer-reviewed publications in the PubMed database through a block search approach using a combination of index MeSH and free text search terms. Publications were considered if they covered biomarkers of prenatal or postnatal exposures to xenobiotic EDCs (European Commission's list of category 1 EDCs) measured in maternal or child biospecimen and pubertal onset defined by the progression of the following milestones (and assessed in terms of the following measures): menarche (age), thelarche (Tanner staging) and pubarche (Tanner staging), in girls, and genital stage (Tanner staging), testicular volume (ml) and pubarche (Tanner staging), in boys.

OUTCOMES: The literature search resulted in 703 references, of which we identified 52 publications fulfilling the eligibility criteria for the qualitative trend synthesis and 23 publications for the meta-analysis. The qualitative trend synthesis provided data on 103 combinations of associations between prenatal or postnatal exposure to EDC compounds groups and puberty outcomes and the meta-analysis enabled 18 summary risk estimates of meta-associations.

WIDER IMPLICATIONS: Statistically significant associations in the qualitative trend synthesis suggested that postnatal exposure to phthalates may be associated with earlier thelarche and later pubarche. However, we did not find consistent evidence in the meta-analysis for associations between timing of pubertal onset in girls and boys and exposures to any of the studied xenobiotic EDCs. We were not able to identify specific pre- or postnatal windows of exposure as particularly critical and susceptible for effects of EDCs. Current evidence is subject to several methodological challenges and inconsistencies and evidence on specific exposure-outcome associations remains too scarce to firmly confirm EDC exposure as a risk factor for changes in age of pubertal onset in the general child population. To create a more uniform foundation for future comparison of evidence and to strengthen pooled studies, we recommend the use of more standardized approaches in the choice of statistical analyses, with exposure transformations, and in the definitions and assessments of puberty outcomes. The impact of mixtures of EDC exposures on the association also remains unestablished and would be valuable to elucidate for prenatal and postnatal windows of exposure. Future large, longitudinal epidemiological studies are needed to clarify the overall association.

Key words: endocrine disrupting chemicals / puberty / menarche / thelarche / pubarche / genital stage / testicular volume / prenatal exposure / postnatal exposure

Introduction

Puberty marks the dynamic transition from childhood to adulthood, during which the child's body undergoes marked physical changes leading to reproductive maturity. In girls, pubertal development commonly starts with breast budding (thelarche) and the first appearance of pubic hair (pubarche) followed by the first menstrual bleeding (menarche) roughly 3 years later, while in boys, testicular enlargement (testicular volume) is usually the first sign of puberty followed by a gradual development of external genitals (genital stage) (Parent *et al.*, 2003). But the onset of pubertal events, and the speed by which puberty progresses, is subject to large interindividual differences. The age of pubertal onset also varies significantly between girls and boys; girls tend to enter puberty at an earlier age (8–13 years) than boys (9–14 years) (Parent *et al.*, 2003). Globally, the age of pubertal onset has, due to largely unknown reasons, decreased substantially during recent decades, especially among girls (Herman-Giddens *et al.*, 1997, 2001; Kaplowitz and Oberfield, 1999; Sun *et al.*, 2002; Wu *et al.*, 2002; Aksglaede *et al.*, 2009; Sørensen *et al.*, 2010). This trend toward earlier puberty is of considerable concern, because earlier onset of pubertal indicators such as age at menarche in girls and voice break in boys have been linked to short- and long-term adverse physical and mental health outcomes including increased risk of obesity (Prentice and Viner, 2013), Type 2 diabetes (Elks *et al.*, 2013; Day *et al.*, 2015), breast cancer (Day *et al.*, 2017) and prostate cancer (Bonilla *et al.*, 2016), as well as depression (Hamlat *et al.*, 2014) and anxiety (Kaltiala-Heino *et al.*, 2003).

The timing of pubertal onset is determined by a variety of genetic factors and environmental influences in addition to gender (Parent *et al.*, 2003). While genetic factors are predominant in determining individual variations in pubertal timing, accounting for ~60% of variations (Sørensen *et al.*, 2013), they cannot explain the observed trend and it is increasingly recognized that non-genetic life style factors like body fat as well as prenatal and postnatal exposures to endocrine disrupting chemicals (EDCs) may play a role in perturbations of pubertal onset (Lucaccioni *et al.*, 2020). An EDC is defined as 'an exogenous substance or mixture that alters the functions of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny' (Bundesumwelt and Kem, 1996). In general, EDCs can be divided into persistent and non-persistent compounds. The persistent EDC compounds are characterized by a long biological half-life period (months to a few years) as they accumulate in body tissue, whereas non-persistent EDC compounds have a relatively short half-life period (hours to days) in the human body (Domínguez-Romero and Scheringer, 2019). It is hypothesized that EDCs can interfere with normal hormone function and metabolism, which can either delay or accelerate the onset of puberty (Lucaccioni *et al.*, 2020).

Several epidemiological studies and a recent systematic review have addressed this issue over the past 10 years. However, evidence of an association between EDCs and changes in pubertal development

remains largely inconclusive due to inconsistency in findings and reporting of both earlier and later pubertal onset (Lee *et al.*, 2019; Castiello and Freire, 2021). To date, no meta-analysis has been conducted and a systematic quantitative and qualitative evaluation of the current epidemiological evidence on effects of environmental endocrine disrupting xenobiotics has become timely. In this systematic review, we aimed to identify and evaluate current evidence on the timing of pubertal onset in girls and boys following prenatal or postnatal exposures to xenobiotic EDCs.

Methods

Study design

A systematic literature review and meta-analysis was performed in accordance with the PRISMA statement for reporting systematic reviews and meta-analyses of observational studies.

Protocol and registration

A review protocol was registered at PROSPERO.org (registration number CRD42021223868) prior to the study. The protocol was approved by all authors.

Search strategy

We performed a systematic search of peer-reviewed original literature in English published prior to 1 February 2021 to identify the available evidence on xenobiotic EDC exposures and changes in pubertal onset in girls and boys. The systematic literature search was conducted in the PubMed database through a block search approach using a combination of index MESH and free text search terms. The identified search terms were divided into two search blocks: the first block covering the exposure (xenobiotic EDCs) and the second block covering the outcome (timing of pubertal onset). We subsequently performed a hand search of the reference lists of the included publications. The search specifications and respective hits in each search block are provided in the search protocol (Supplementary Table SI).

Eligibility criteria

Publications were considered eligible if the following criteria were met.

Xenobiotic EDCs

Xenobiotic EDCs were defined as an exogenous man-made chemical or a mixture of chemicals that have been included in the European Commission's list of Category 1 EDCs (McCarthy, 2011) and measured in maternal (prenatal or proxy of prenatal) or child (postnatal) biospecimens. Throughout the manuscript, we use the term 'exposure' to represent the use of exposure biomarkers. The following 11 compound groups of EDCs were investigated in the included publications: (i) benzophenones and other UV filters (hereafter UV filters); (ii) bisphenol A (hereafter BPA); (iii) dioxins; (iv) flame retardants; (v) parabens; (vi) phthalates diesters and their metabolites (hereafter phthalates); (vii) polyaromatic hydrocarbons (hereafter PAHs); (viii) polychlorinated biphenyl (hereafter PCBs); (ix) polychlorinated phenols/organochloride pesticides (hereafter polychlorinated phenols/pesticides); (x) polyfluoroalkyl chemicals/per- and polyfluoroalkyl substances (hereafter PFCs/PFAS) and (xi) triclosan.

Pubertal onset

Pubertal onset was defined by the timing of the progression of the following pubertal milestones: menarche (age of first bleed), thelarche (Tanner staging), pubarche (Tanner staging), in girls, and genital stage (Tanner staging), testicular volume (ml) and pubarche (Tanner staging), in boys. Puberty outcomes using Tanner staging were determined by clinical assessments (visual inspection and/or palpitation) or self-report according to the Tanner scale, in which Stage 1 represents the prepubertal state and entrance into Stage 2 represents the onset of puberty (Marshall and Tanner, 1969). In girls, pubertal onset (B2+), a phenomenon also termed thelarche, is followed by subsequent breast enlargement corresponding to Tanner breast Stages B2 to B5. Menarche was assessed by retrospective self-report at the time of interview or via a diary completed prior to first bleed (exact age). In boys, pubertal onset is denoted by entrance into Tanner genital Stage 2 (G2+), followed by testicular/penis enlargement throughout genital Stage G2 to G5. Testicular volume was assessed by clinical assessment using orchidometer or ultrasound. For both sexes, appearance of pubic hair (curly pigmented hair) denotes Tanner pubic hair stage PH2 (a phenomenon termed pubarche), which usually occurs concurrently with gonadarche, i.e. breast or genital development. However, isolated pubic hair development may represent adrenal androgen secretion (a phenomenon termed adrenarche), which is not always associated with simultaneous activation of the hypothalamo-pituitary-gonadal hormone axis. However, it is not possible to distinguish gonadarche from adrenarche without thorough biochemical evaluation.

Exclusion criteria

Publications prior to 1 January 1990 or publications covering non-human studies, case-reports, experimental studies, reviews, conference proceedings/abstracts, letters, editorials and comments were excluded. We also excluded publications addressing natural estrogens (e.g. phytoestrogens or prescription hormones), publications not reporting risk estimates or duplicates repeating estimates reported in previous publications.

Selection of literature

We obtained 703 search references after removal of duplicates, including 11 references identified through hand searches and reference lists (Fig. 1). Titles and abstracts were screened by two authors (T.K. and C.S.O.) independently to assess eligibility. A total of 107 publications were considered eligible for full-text assessments. Among these, 55 publications were eventually excluded as they did not fulfill the defined eligibility criteria, such as exposure not measured in biospecimen (n = 9) or outcome defined as idiopathic central precocious puberty (n = 16). A total of 52 publications were included in the final review and qualitative trend synthesis. Of these, 23 publications were found eligible for the meta-analysis according to eligibility criteria.

Assessment of quality

The quality of the included publications was assessed to enable a critical interpretation of the respective study findings. All 52 publications

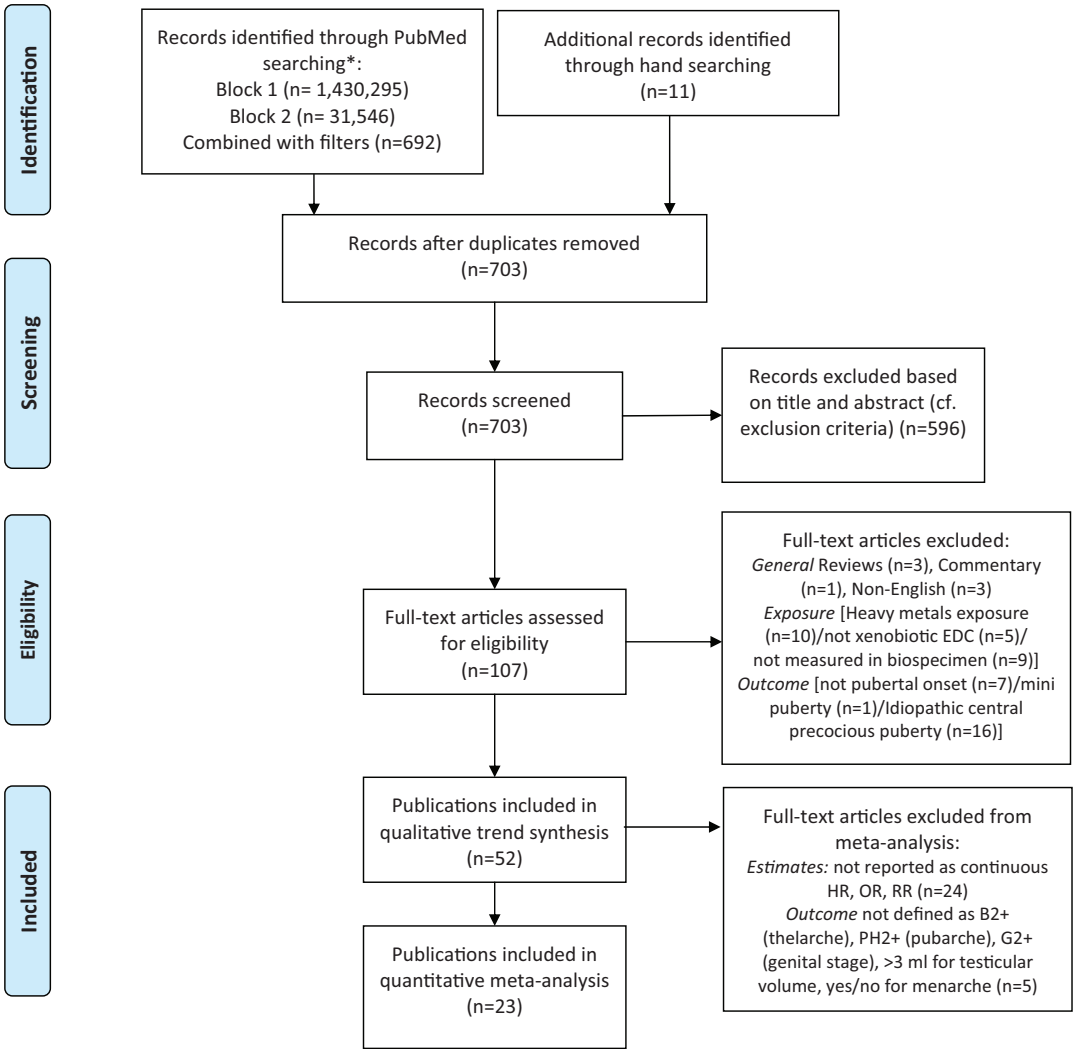

Figure 1. Flow diagram of the identified English publications prior to 1 February 2021.

were evaluated for completeness of reporting and potential sources of bias using a standardized form adapted from Bonzini *et al.* (2007) and Shamliyan *et al.* (2010). (The evaluation form is available in Supplementary Table SII.) The publications were evaluated independently by two authors (T.K. and C.S.O.) and any discrepancies in scoring were resolved through discussions with a third author (E.V.B.).

Completeness of reporting was assessed in the following 11 areas: (i) study design; (ii) sampling frame and procedures; (iii) inclusion and exclusion; (iv) population characteristics of exposed/unexposed or cases/referents; (v) response rate reported or implicitly given; (vi) methods for exposure measurement; (vii) method for outcome ascertainment; (viii) external quality assurance program of biochemical analyses; (ix) detection level and precision for biological samples; (x) statistical analysis and (xi) exposure-response. The 11 areas were equally weighted with the value one given for adequate reporting. We considered a sum of $\geq$8 as sufficient completeness of reporting.

Potential sources of bias were evaluated in seven areas, of which the following four areas were considered the most critical sources of bias and included for final assessment: (i) reporting of tested hypotheses; (ii) selection bias from loss of follow-up or lack of representativeness in a population sample; (iii) information bias related to outcome ascertainment and (iv) accounting for confounding. Each of the four areas were either rated as high risk, uncertain risk or low risk. Publications were considered at higher risk of bias if two or more of the given areas were identified as high risk of bias.

Data extraction and qualitative trend synthesis

Descriptive characteristics were extracted from each publication including study period, location, age at interview/examination, study design, sample size, biospecimens, outcome specifications, EDCs

examined, exposure window, etc. In a qualitative trend synthesis, the identified characteristics were presented in a table separately for girls and boys according to prenatal or postnatal exposure compounds along with a direction of the association between exposure and pubertal onset (regardless of statistical significance of the estimate) illustrated by arrows: downward pointing arrow indicating earlier onset; upward pointing arrow indicating later; and a horizontal arrow indicating no association (Tables II and III). The assigned assessment scores for completeness of reporting and risk of bias for individual publications were also presented. In a supplementary synthesis, the direction of all trends was presented according to each individual compound (rather than by publication) for girls and boys combined (Supplementary Table SIII). A risk of bias graph of all publications was also visualized in a separate figure (Fig. 2).

Meta-analysis

The meta-analysis provided summary risk estimates between specific exposures to EDCs and changes in pubertal onset in girls and boys. We applied a stepwise approach addressing three different strategies for grouping exposure compounds (Table I) separately for prenatal and postnatal exposures: (i) the associations according to compound groups of EDCs and timing of pubertal onset in girls and boys (main analysis); (ii) the associations according to persistent and non-persistent EDC groups and timing of pubertal onset in girls and boys; and (iii) the associations according to chemicals obtained on the EU REACH 2020 (European Chemicals Agency, 2021a) and/or 2021 Substances of Very High Concern (SVHC) lists (European Chemicals Agency, 2021b) and timing of pubertal onset in girls and boys.

The three strategies attempted to address the effects of groups and multiple combined EDC compounds that would be expected in real life, but we acknowledge that individual compounds within the classes may vary in potency. Further, the biological activity may vary, for instance with some EDCs being estrogenic, while others having been shown to possess anti-androgenic properties, or even both.

Publications were only included in the meta-analysis if the estimates were reported as a relative risk (RR; odds ratio, hazard ratio or risk ratio) associated with exposure contrast (Hartemink *et al.*, 2006; Hagan *et al.*, 2011) and if the outcome was defined as Tanner stage $\geq$2 for thelarche (B2+), pubarche (PH2+) or genital stage (G2+); >3 ml for testicular volume; or yes/no for menarche.

Within each strategy, separate forest plots for each puberty outcome stratified by prenatal or postnatal exposure to specific compounds were created to illustrate summary RRs with 95% CIs. We standardized risk estimates to a common log scale ($\log_{10}$(RR)) prior to analyses, as many EDC exposures had been reported as estimates based on various log scales (e.g. $\log_2$, $\log_{10}$, natural $\log_e$) due to lack of normal distribution. We used a 10-fold exposure increase to identify small differences. Exposure-outcome summary risk estimates in the meta-analyses were only provided if multiple publications (at least two) were available and if three or more individual exposure-outcome estimates were available. We pooled the risk estimates by a random-effect meta-analysis and computed a common summary risk estimate by weighting the risk estimates with the inverse variance (within-study and between-studies) computed from the provided confidence limits. A formal measure of heterogeneity was provided using I^2 statistics. All statistical analyses were performed using R (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) with a significance level of 0.05.

Results

Study base

We identified 52 publications (Blanck *et al.*, 2000; Vasiliu *et al.*, 2004; Warner *et al.*, 2004, 2020; Denham *et al.*, 2005; Ouyang *et al.*, 2005; Leijs *et al.*, 2008; Wolff *et al.*, 2008, 2010, 2014, 2015, 2017; Small *et al.*, 2009; Chen *et al.*, 2011; Christensen *et al.*, 2011; Den Hond *et al.*, 2011; Humblet *et al.*, 2011; Korrick *et al.*, 2011; Lopez-Espinosa *et al.*, 2011; Buttke *et al.*, 2012; Frederiksen *et al.*, 2012; Grandjean *et al.*, 2012; Mouritsen *et al.*, 2013; Ferguson *et al.*, 2014; Lam *et al.*, 2014; Watkins et al., 2014, 2017a,b; Hou *et al.*, 2015; McGuinn *et al.*, 2015; Shi *et al.*, 2015; Su *et al.*, 2015; Windham *et al.*, 2015; Zhang

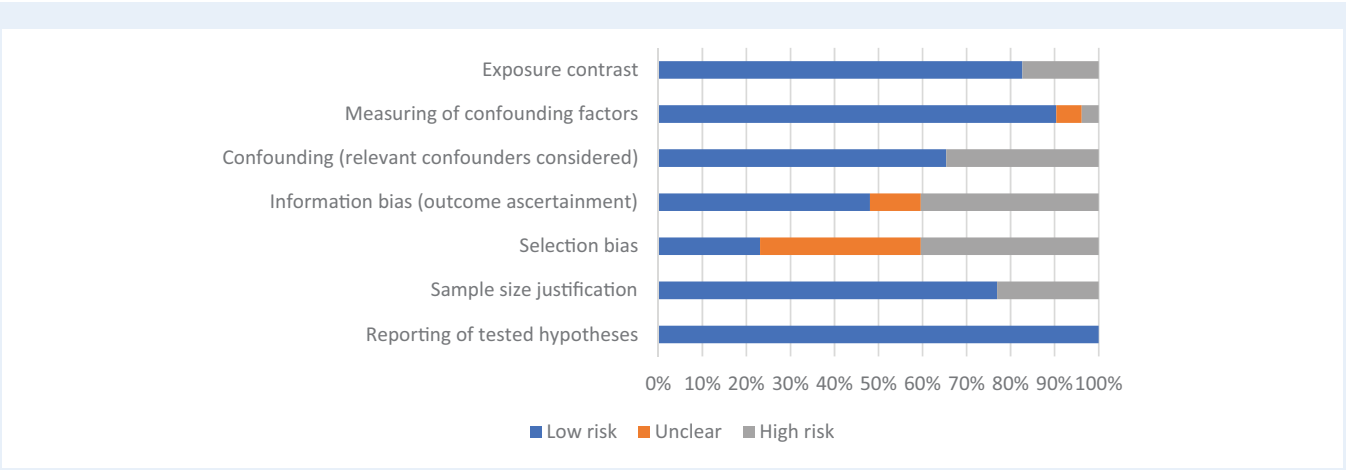

Figure 2. Risk of bias. The proportion of included publications with each of the identified risk categories (low risk, uncertain risk and high risk).

Table I List of specific chemical substances and abbreviations.

Individual EDC compounds	Abbreviation	EDC groupings	Included in meta-analysis		
			Strategy 1	Strategy 2	Strategy 3
			EDC grouping	Persistent/ non-persistent	REACH 2020 and SVHC 2021
Benzophenone-2	BP-2	Benzophenones and other UV filters	×	×non-persistent	
Benzophenone-3	BP-3	Benzophenones and other UV filters	×	×non-persistent	
Ethyl-hexyl methoxycinnamate	EHMC	Benzophenones and other UV filters	×	×persistent	
4′-methoxyacetophenone	4′-MAP	Benzophenones and other UV filters	×	×persistent	
Ethylhexyl dimethyl PABA	OD-PABA	Benzophenones and other UV filters	×	×persistent	
Bisphenol A	BPA	Bisphenol A	×	×non-persistent	×
Bisphenol A-G	BPA-G	Bisphenol A	×	×non-persistent	×
Polychlorinated dibenzo-p-dioxins	PCDD	Dioxins			
Polychlorinated dibenzo-p-furans	PCDF	Dioxins			
2,3,7,8-Tetrachlorodibenzo-p-dioxins	TCDD	Dioxins		×persistent	×
Polybrominated biphenyl	PBB	Flame retardants			
2,4,4′-Tribromodiphenyl ether	BDE-28	Flame retardants	×	×persistent	×
2,2′,4,4′-Tetrabromodiphenyl ether	BDE-47	Flame retardants	×	×persistent	×
2,2′,4,4′,5-Pentabromodiphenyl ether	BDE-99	Flame retardants	×	×persistent	×
2,2′,4,4′,6-Pentabromodiphenyl ether	BDE-100	Flame retardants	×	×persistent	×
2,2′,4,4′,5,5′-Hexabromodiphenyl ether	BDE-153	Flame retardants	×	×persistent	×
2,2′,4,4′,5,6′-Hexabromodiphenyl ether	BDE-154	Flame retardants	×	×persistent	×
Methyl paraben	MePB	Parabens		×non-persistent	
Propyl paraben	PrPB	Parabens		×non-persistent	×
Mono-methyl phthalate [DMP metabolite]	MMP	Phthalate diesters and their metabolites	×	×non-persistent	
Mono-ethyl phthalate [DEP metabolite]	MEP	Phthalate diesters and their metabolites	×	×non-persistent	
Mono-iso-butyl phthalate [DiBP metabolite]	MiBP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(2-hydroxy-iso-butyl) phthalate [DiBP metabolite]	2OH-MiBP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-n-butyl phthalate [DnBP metabolite]	MnBP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(3-hydroxybutyl) phthalate [DnBP metabolite]	3OH-MnBP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-benzyl phthalate [BBzP metabolite]	MBzP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(2-ethyl-hexyl) phthalate [DEHP metabolite]	MEHP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(2-ethyl-5-hydroxyhexyl) phthalate [DEHP metabolite]	5OH-MEHP Alternative: MEHHP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(2-ethyl-5-oxohexyl) phthalate [DEHP metabolite]	5oxo-MEHP Alternative: MEOHP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(2-ethyl-5-carboxypentyl) phthalate [DEHP metabolite]	5cx-MEPP Alternative: MECPP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-3-carboxylpropyl phthalate [DnOP metabolite, non-specific]	MCPP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-iso-nonyl phthalate [DiNP metabolite]	MiNP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-hydroxy-iso-nonyl phthalate [DiNP metabolite]	OH-MiNP Alternative: MHiNP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-oxo-iso-nonyl phthalate [DiNP metabolite]	oxo-MiNP Alternative: MOiNP	Phthalate diesters and their metabolites	×	×non-persistent	×

Continued

Table 1 Continued

Individual EDC compounds	Abbreviation		EDC groupings	Included in meta-analysis		
				Strategy 1	Strategy 2	Strategy 3
				EDC grouping	Persistent/ non-persistent	REACH 2020 and SVHC 2021
Mono-carboxy-iso-octyl phthalate [DiNP metabolite]	cx-MiOP	Alternative: MCiOP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(hydroxy-iso-decyl) phthalate [DiDP metabolite]	OH-MiDP	Alternative: MHiDP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(oxo-iso-decyl) phthalate [DiDP metabolite]	oxo-MiDP	Alternative: MOiDP	Phthalate diesters and their metabolites	×	×non-persistent	×
Mono-(carboxy-iso-nonyl) phthalate [DiDP metabolite]	cx-MiNP	Alternative: MCiNP	Phthalate diesters and their metabolites	×	×non-persistent	×
Polychlorinated biphenyl		PCB	Polychlorinated biphenyl		×persistent	×
2,4-dichlorophenol		2,4-DCP	Polychlorinated phenols/organochloride pesticides		×non-persistent	
2,5-dichlorophenol		2,5-DCP	Polychlorinated phenols/organochloride pesticides		×non-persistent	
1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene		DDE	Polychlorinated phenols/organochloride pesticides		×persistent	×
2,2-Bis(4-chlorophenyl)-1,1-dichloroethylene		*p,p′*-DDE	Polychlorinated phenols/organochloride pesticides			
1,1′-(2,2,2-Trichloroethane-1,1-diyl)bis(4-chlorobenzene)		DDT	Polychlorinated phenols/organochloride pesticides		×persistent	×
1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene		*p,p′*-DDT	Polychlorinated phenols/organochloride pesticides		×persistent	×
Hexachlorobenzene		HCB	Polychlorinated phenols/organochloride pesticides		×persistent	×
Beta-hexachlorobenzene		*β*-HCB	Polychlorinated phenols/organochloride pesticides			
Beta-hexachlorocyclohexane		*β*-HCH	Polychlorinated phenols/organochloride pesticides			
3-phenoxybenzoic acid [metabolite of pyrethroid]		3-PBA	Polychlorinated phenols/organochloride pesticides			
Perfluorohexane sulfonate		PFHxS	PFCs or PFAS		×persistent	×
Perfluorononanoate		PFNA	PFCs or PFAS		×persistent	×
Perfluorooctanoic acid		PFOA	PFCs or PFAS		×persistent	×
Perfluorooctane sulfonic acid		PFOS	PFCs or PFAS		×persistent	×
Perfluorooctane sulfonamide		PFOSA	PFCs or PFAS		×persistent	×
2-(N-ethyl-perfluorooctane sulfonamido) acetate		Et-PFOSA-AcOH	PFCs or PFAS		×persistent	×
2-(N-methyl-perfluorooctane sulfonamido) acetate		Me-PFOSA-AcOH	PFCs or PFAS		×persistent	×
Triclosan		TCS	Triclosan	×	×non-persistent	

EDC, endocrine disrupting chemical.

Table II Study characteristics and qualitative trend synthesis for associations between prenatal or postnatal exposures to endocrine disrupting chemicals and menarche, M (age, n = 31 publications), thelarche, T (Tanner staging, n = 25 publications) and pubarche, P (Tanner staging, n = 23 publications) in girls.

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔None					
Prenatal exposure														
Benzophenones	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	172	Urine	BP-3	↓	↓	↑	10	0	No
Bisphenol A	Berger *et al.* (2018)	USA	1999–2000	9	Longitudinal cohort	537	Urine	BPA	↑	↑*	↑	8	0	No
	Watkins *et al.* (2014)	Mexico	1997–2004	8–13	Longitudinal cohort	116	Urine	BPA	↑	↓	↓	7	1	No
	Watkins *et al.* (2017b)	Mexico	1997–2004	8–13	Longitudinal cohort	120	Urine	BPA	↑	↓	↓	8	1	No
Dioxins	Leijs *et al.* (2008)[#]	Netherlands	2005–2006	14–19	Longitudinal cohort	30	Breast milk	PCDF		↑*		8	1	No
	Warner *et al.* (2020)	Italy	1996	8–39	Longitudinal cohort	316	Serum	TCDD	↑			8	1	No
Flame retardants (Polybrominated diphenyl ethers, PBDE)	Blanck *et al.* (2000)[#]	USA	1976–1979	5–24	Longitudinal cohort	327	Serum	PBB	↓	↓	↓*	10	1	No
	Harley *et al.* (2017)	USA	1999–2000	9	Longitudinal cohort	140	Serum	BDE-47	↑*	↑	↑	10	0	No
								BDE-99	↑*	↔	↔			
								BDE-100	↑*	↑	↔			
								BDE-153	↑*	↑	↑			
								∑PBDE	↑*	↑	↑			
Parabens	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	172	Urine	MePB	↓	↑	↑	10	0	No
								PrPB	↓	↑	↑			
Phthalate diesters and their metabolites	Berger *et al.* (2018)	USA	1999–2000	9	Longitudinal cohort	537	Urine	MBzP	↑	↑*	↑	8	0	No
								MCPP	↑	↑	↑			
								cx-MiOP	↑	↑	↑			
								cx-MiNP	↑	↑	↑			
								∑DEHPm**	↑*	↑*	↑			
	Cathey *et al.* (2020)	Mexico	1997–2004	8–14	Longitudinal cohort	103	Urine	MEP	↓	↓	↓	8	1	No
								MiBP	↔	↓	↑			
								MnBP	↓	↓	↓			
								MBzP	↓	↓*	↓			
								MEHP	↓	↓	↓			
								5OH-MEHP	↓	↓*	↓			
								5oxo-MEHP	↓	↓*	↓			
								5cx-MEPP	↓	↓*	↓			
								MCPP	↓	↓	↓			
								∑DEHPm**	↓	↓*	↓			
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	172	Urine	MEP	↓	↓	↓*	10	0	No
								MiBP	↓	↓	↓			
								MnBP	↓	↓	↑			

Continued

Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
	Watkins *et al.* (2014)	Mexico	1997–2004	8–13	Longitudinal cohort	116	Urine	MEP	↓	↓	↓	7	1	Yes$^{(M,T,P)}$
								MiBP	↑	↑	↓			
								MnBP	↑	↑	↓			
								MBzP	↑	↓	↓			
								MEHP	↑	↑	↓*			
								5OH-MEHP	↓	↑	↓			
								5oxo-MEHP	↓	↑	↓			
								5cx-MEPP	↓	↑	↓			
								MCPP	↓	↓	↓			
	Watkins *et al.* (2017b)	Mexico	1997–2004	8–13	Longitudinal cohort	120	Urine	MEP	↓*	↓	↓	8	1	Yes$^{(M,T,P)}$
								MiBP	↑	↓	↓			
								MnBP	↑	↓	↓			
								MBzP	↑	↓	↓			
								MEHP	↑	↑*	↓			
								MCPP	↔	↓	↓			
								∑DEHPm**	↓	↑	↓			
Polychlorinated biphenyl (PCB)	Vasiliu *et al.* (2004)	USA	1973–1991	20–50	Longitudinal cohort	151	Serum	∑PCB	↓			10	1	No
Polychlorinated phenols/ organochloride pesticides	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	172	Urine	2,4-DCP	↓*	↓	↓	10	0	No
								2,5-DCP	↓	↓	↓			
	Namulanda *et al.* (2016)	England	1991–1992	8–17	Nested case–control	218/230	Serum	*p,p'*-DDT	↑			10	1	No
								HCB	↑					
								β-HCB	↑					
	Namulanda *et al.* (2017)	England	1991–1992	8–17	Nested case–control	174/195	Urine	D-atrazine	↓*			10	1	No
	Vasiliu *et al.* (2004)	USA	1973–1991	20–50	Longitudinal cohort	151	Serum	DDE	↓*			10	1	No
Polyfluoroalkyl chemicals/ per- and polyfluoroalkyl substances	Christensen *et al.* (2011)	England	1991–1992	8–13	Nested case–control	218/230	Serum	Carboxylates	↑			9	1	No
								PFHxS	↑					
								PFNA	↑					
								PFOA	↓					
								PFOS	↑					
								PFOSA	↑					
								Et-PFOSA-ACOH	↓					
								Me-PFOSA-ACOH	↑					
								sulfonamide esters	↑					
								sulfonates	↑					
	Ernst *et al.* (2019)[#]	Denmark	1996–2002	11	Longitudinal cohort	555	Serum	PFOA	↓	↓	↑	10	1	No
								PFOS	↓	↓	↑			
Triclosan	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	172	Urine	TCS	↓*	↓	↔	10	0	No

Continued

Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
Postnatal exposure														
Benzophenones and other UV filters	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	BP-3	↓			8	0	Yes$^{(M)}$
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	BP-3	↑			9	0	Yes$^{(M)}$
	Harley *et al.* (2019]	USA	1999–2000	9	Longitudinal cohort	155	Urine	BP-3	↓	↓	↓	10	0	No
	Huang *et al.* (2020)$_{(baseline)}$	China	2011	7–15	Cross-sectional	244	Urine	BP-2	↓	↑	↔	8	0	Yes$^{(M)}$
								BP-3	↓	↑	↓			
								EHMC	↓	↑	↔			
								4'-MAP	↓	↑	↓			
								OD-PABA	↑	↓	↓			
	Huang *et al.* (2020)$_{(18\ months\ follow\text{-}up)}$		+18 months	+18 months		176		BP-2	↓	↔	↓			
								BP-3	↔	↓	↑			
								EHMC	↑	↔	↑			
								4'-MAP	↑	↔	↓			
								OD-PABA	↓	↓	↓*			
	Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	BP-3		↓	↓	8	0	No
	Wolff *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	BP-3		↑*	↔	8	I	No
	Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	BP-3	↑			8	I	Yes$^{(M)}$
Bisphenol A	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	BPA	↑			8	0	Yes$^{(M)}$
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	BPA	↑			9	0	Yes$^{(M)}$
	Howland *et al.* (2020)[#]	UK	2009–2011	5–16	Cross-sectional	348	Urine	BPA-G		↓		8	I	Yes$^{(T)}$
	Kasper-Sonnenberg *et al.* (2017)[#]	Germany	2009–2010	8–10	Longitudinal cohort	222	Urine	BPA	↓	↑	↓	7	I	Yes$^{(M)}$
	McGuinn *et al.* (2015)	USA	2003–2010	12–19	Cross-sectional	987	Urine	BPA	↑			9	0	Yes$^{(M)}$
	Miao *et al.* (2017)	China	2011	9–18	Cross-sectional	655	Urine	BPA	↑*	↑	↓	8	0	No
	Watkins *et al.* (2014)	Mexico	1997–2004	8–13	Longitudinal cohort	116	Urine	BPA	↑	↑	↑	7	I	Yes$^{(M,T,P)}$
	Wolff *et al.* (2008)	USA	1996–1997	9	Cross-sectional	186	Urine	BPA		↑	↑	8	0	Yes$^{(T,P)}$
	Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	BPA		↑	↔	8	0	No
	Wolff *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	BPA		↑	↓	8	I	Yes$^{(T,P)}$
	Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	BPA	↓			8	I	Yes$^{(M)}$
Dioxins	Warner *et al.* (2004)	Italy	1996–1998	NR	Retrospective cohort	282	Serum	TCDD	↑			9	0	No
Flame retardants (Polybrominated diphenyl ethers, PBDE)	Attfield *et al.* (2019)	USA	2004–2007	6–8	Longitudinal cohort	1257	Serum	∑PBDE	↑			10	0	No
	Chen *et al.* (2011)	USA	2003–2004	12–19	Cross-sectional	271	Serum	BDE-28	↓*			9	0	Yes$^{(M)}$
								BDE-47	↓*					
								BDE-99	↓*					
								BDE-100	↓*					
								BDE-153	↓*					
								BDE-154	↓*					
								∑PBDE	↓*					

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Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔None					
	Harley *et al.* (2017)	USA	1999–2000	9	Longitudinal cohort	266	Serum	BDE-47	↑	↑	↔	10	1	Yes[(M)]
								BDE-99	↑	↑	↔			
								BDE-100	↑	↑	↑			
								BDE-153	↑	↑	↑			
								∑PBDE	↑	↑	↔			
	Windham *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	645	Serum	∑PBDE		↑*	↑*	8	0	No
Parabens	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	MePB	↔			8	0	No
								PrPB	↑					
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	∑parabens	↑			9	0	No
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	MePB	↓*	↓*	↓*	10	0	No
								PrPB	↓	↓	↓*			
	Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	∑parabens		↓	↑	8	0	No
	Wolff *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	∑parabens		↓	↓	8	1	No
	Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	∑parabens	↓			8	1	No
Phthalate diesters and their metabolites	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	MMP	↓			8	0	Yes[(M)]
								MEP	↓					
								MiBP	↓					
								2OH-MiBP	↓					
								MnBP	↑					
								MBzP	↑					
								MEHP	↓					
								5OH-MEHP	↓					
								5oxo-MEHP	↓					
								5cx-MEPP	↓					
								MCPP	↑					
								cx-MiOP	↑					
								cx-MiNP	↑					
								∑DEHPm**	↓					
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	∑phthalates	↑			9	0	No
	Frederiksen *et al.* (2012)	Denmark	2006–2008	6–19	Cross-sectional	725	Urine	MEP		↓	↑	9	1	No
								MiBP+MnBP		↓	↑*			
								MBzP		↑	↑*			
								∑DEHPm**		↑	↑			
								∑DiNPm**		↑	↑			
								∑phthalates		↑	↑*			
								∑corr.phthalates		↑				

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Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔None					
	Hou *et al.* (2015)[#]	Taiwan	2012–2003	7–15	Cross-sectional	270	Urine	MMP	↑	↔	↑	9	I	No
								MEP	↔	↑	↔			
								MiBP	↔	↓	↓			
								MnBP	↓	↓	↓			
								MBzP	↔	↓	↑			
								MEHP	↑	↑	↑			
								5OH-MEHP	↓	↓	↓			
								5oxo-MEHP	↓	↑	↑			
								5cx-MEPP	↓	↓	↓			
								∑DEHPm**	↓	↑	↑			
								∑low-MWP	↑	↓	↓			
								∑high-MWP	↓	↑	↑			
								∑phthalates	↑					
	Kasper-Sonnenberg *et al.* (2017)[#]	Germany	2009–2010	8–10	Longitudinal cohort	222	Urine	MMP	↑	↑	↑	7	I	Yes[(M)]
								MEP	↑	↑*	↑			
								MiBP	↓	↑	↑			
								2OH-MiBP	↑	↑	↓			
								MnBP	↑	↑	↑			
								3OH-MnBP	↑	↑	↓			
								MBzP	↑	↑	↓			
								MEHP	↑	↑	↑			
								5OH-MEHP	↑	↑	↑			
								5oxo-MEHP	↑	↑	↑			
								5cx-MEPP	↑	↑	↑			
								MiNP	↑	↓*	↓*			
								OH-MiNP	↓	↓	↓			
								oxo-MiNP	↓	↓	↓			
								cx-MiOP	↓	↓	↑			
								OH-MiDP	↑	↓	↓			
								oxo-MiDP	↑	↓	↓			
	Mouritsen *et al.* (2013)	Denmark	2006–2010	6–13	Longitudinal cohort	84	Urine	MEP		↑	↔	8	I	No
								MiBP + MnBP		↑	↑			
								MBzP		↓	↔			
								∑DEHPm**		↓	↔			
								∑DiNPm**		↔	↑			
								∑corr.phthalates		↑	↑			

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Table II Continued

Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
								↓ Earlier ↑ Later ↔None					
Shi *et al.* (2015)	China	2010	7–14	Cross-sectional	186	Urine	MMP	↓	↑	↑	10	1	Yes$^{(M)}$
							MEP	↓	↔	↓			
							MnBP	↑	↓	↓			
							MEHP	↑	↓*	↓			
							5OH-MEHP	↑	↓*	↔			
							5oxo-MEHP	↑	↓*	↓			
							∑DEHPm**	↑	↓*	↓			
Watkins *et al.* (2014)	Mexico	1997–2004	8–13	Longitudinal cohort	116	Urine	MEP	↓	↓	↓	7	1	Yes$^{(M,T,P)}$
							MiBP	↓	↓	↓			
							MnBP	↓	↓	↓			
							MBzP	↓	↓	↓			
							MEHP	↑	↓	↓			
							5OH-MEHP	↓	↓	↓			
							5oxo-MEHP	↓	↓	↓			
							5cx-MEPP	↓	↓	↓			
							MCPP	↑	↓	↓			
Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	∑low-MWP		↓	↓	8	0	No
							∑high-MWP		↓	↑			
Wolff *et al.* (2014)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	MEP		↓	↑	8	0	Yes$^{(T,P)}$
							MiBP		↑	↑			
							MnBP		↑	↑			
							MBzP		↑	↑*			
							MEHP		↓	↑*			
							5OH-MEHP		↓	↑*			
							5oxo-MEHP		↓	↑*			
							5cx-MEPP		↓	↑			
							MCPP		↓	↑			
							∑DEHPm**		↓	↑*			
							∑low-MWP		↓	↑			
							∑high-MWP		↑	↑*			
Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	MEP	↓			8	1	Yes$^{(M)}$
							MiBP	↓					
							MnBP	↑					
							MBzP	↑					
							MEHP	↑					
							5OH-MEHP	↑					
							5oxo-MEHP	↑					
							5cx-MEPP	↓					
							MCPP	↑*					
							∑DEHPm**	↔					
							∑low-MWP	↓					
							∑high-MWP	↑					

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Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔None					
	Zhang *et al.* (2015)(baseline)	China	2011	7–14	Cross-sectional	251	Urine	MMP	↑	↑	↑	10	0	Yes[(M,T,P)]
								MEP	↓	↓	↓			
								MnBP	↑	↑	↑			
								MEHP	↑	↓	↓			
								5OH-MEHP	↑	↓	↑			
								5oxo-MEHP	↑	↓	↓			
								∑DEHPm**	↑	↓	↑			
	Zhang *et al.* (2015)(18 months follow-up)		+18 months	+18 months		208		MMP	↑	↓	↓			
								MEP	↑	↑	↓			
								MnBP	↓	↓	↑			
								MEHP	↓	↓*	↑			
								5OH-MEHP	↓	↓*	↑			
								5oxo-MEHP	↓	↓*	↑			
								∑DEHPm**	↓	↓*	↑			
Polyaromatic hydrocarbons (PAH)	Dobraca *et al.* (2020)	USA	2005–2006	6–8	Longitudinal cohort	404	Urine	∑fluorene		↑	↑	8	0	No
								1-hydroxypyrene		↓	↓			
								2-naphthol		↓	↓			
								∑PAH		↓	↔			
								∑phenanthrene		↓	↑			
Polychlorinated biphenyl (PCB)	Attfield *et al.* (2019)	USA	2004–2007	6–8	Longitudinal cohort	1257	Serum	∑PCB	↑			10	0	No
	Denham *et al.* (2005)	Canada	1996–2000	10–17	Cross-sectional	138	Serum	estrogenic ∑PCB	↓*			7	0	No
	Den Hond *et al.* (2011)	Belgium	2003–2004	14–15	Cross-sectional	636	Serum	∑PCB	↑*			9	1	No
	Windham *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	645	Serum	∑PCB			↑	8	0	No
	Wolff *et al.* (2008)	USA	1996–1997	9	Cross-sectional	186	Urine	∑PCB		↑	↓	8	0	No
Polychlorinated phenols/ organochloride pesticides (OCP)	Attfield *et al.* (2019)	USA	2004–2007	6–8	Longitudinal cohort	1257	Serum	∑OCP	↑			10	0	No
	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	2,4-DCP	↔			8	0	Yes[(M)]
								2,5-DCP	↓					
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	2,4-DCP	↓			9	0	Yes[(M)]
								2,5-DCP	↓*					
								∑phenols	↓*					
	Denham *et al.* (2005)	Canada	1996–2000	10–17	Cross-sectional	138	Serum	*p,p'*-DDE	↑			7	0	No
								HCB	↓					
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	2,4-DCP	↓	↑	↑	10	0	No
								2,5-DCP	↑	↑	↑*			
	Hou *et al.* (2015)[#]	Taiwan	2012–2013	7–15	Cross-sectional	270	Urine	nonylphenol	↔	↑	↓	9	1	No
	Ouyang *et al.* (2005)	China	1996–1998	20–34	Cross-sectional	466	Serum	DDT	↓*			10	1	No

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Table II Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	M	T	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
	Windham *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	645	Serum	∑OCP		↑	↑	8	0	No
	Wolff *et al.* (2008)	USA	1996–1997	9	Cross-sectional	186	Serum	DDE		↓	↓	8	0	No
	Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	2,5-DCP		↓	↑	8	0	No
	Wolff *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	2,5-DCP		↓*	↓*	8	1	No
	Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	2,5-DCP	↓			8	1	Yes$^{(M)}$
	Ye *et al.* (2017)[#]	China	2014–2015	9–15	Cross-sectional	305	Urine	3-PBA	↑*	↑	↑*	9	0	No
Polyfluoroalkyl chemicals/ per- and polyfluoroalkyl substances	Lopez-Espinosa *et al.* (2011)	USA	2005–2006	8–18	Cross-sectional	2931	Serum	PFOA	↑*			11	1	No
								PFOS	↑*					
Triclosan	Binder *et al.* (2018)	Chile	2009	7–10	Longitudinal cohort	200	Urine	TCS	↔			8	0	Yes$^{(M)}$
	Buttke *et al.* (2012)	USA	2003–2008	12–16	Cross-sectional	461	Urine	TCS	↑			9	0	Yes$^{(M)}$
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	TCS	↑	↔	↑	10	0	No
	Wolff *et al.* (2010)	USA	2004–2007	6–8	Longitudinal cohort	1151	Urine	TCS		↓	↑	8	0	No
	Wolff *et al.* (2015)	USA	2004–2007	6–8	Longitudinal cohort	1170	Urine	TCS		↓*	↓	8	1	No
	Wolff *et al.* (2017)	USA	2004–2007	6–8	Longitudinal cohort	1051	Urine	TCS	↓			8	1	Yes$^{(M)}$

[↑]Later onset; [↓]Earlier onset; ↔ none detected

[#]Self-reported thelarche or pubarche rather than clinical examination (age at menarche is self-reported in all publications)

[§]CR: Completeness of reporting ≥8 was considered sufficient; Bias and confounding: 1 = potential risk of bias, 0 = lower risk of bias

*P-value <0.05

$^{(M,T,P)}$Included in meta-analysis for menarche (M); thelarche (T); pubarche (P)

** Sums of selected phthalate mewtabolites and substitutes:

∑DEHPm: molar sum of MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP and 2cx-MMHP expressed as DEHP

∑DiNPm: molar sum of MiNP, OH-MiNP, oxo-MiNP and cx-MiOP expressed as DiNP

low/high MWP: low/high molecular weight phthalates

EDC, endocrine disrupting chemical.

Table III Study characteristics and qualitative trend synthesis for associations between prenatal or postnatal exposures to endocrine disrupting chemicals and genital stage, GS (Tanner staging, n = 17), testicular volume, TV (ml, n = 15) and pubarche, P (Tanner staging, n = 20) in boys.

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	GS	TV	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
Prenatal exposure														
Benzophenones	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	BP-3	↑		↑	10	0	No
Bisphenol A	Berger *et al.* (2018)	USA	1999–2000	9	Longitudinal cohort	537	Urine	BPA	↓*		↓*	8	0	No
	Ferguson *et al.* (2014)	Mexico	1994–2004	8–14	Longitudinal cohort	107	Urine	BPA	↑	↓	↑	7	1	No
	Watkins *et al.* (2017a)	Mexico	1997–2004	8–14	Longitudinal cohort	109	Urine	BPA	↓	↓	↑	7	1	No
Dioxins	Humblet *et al.* (2011)[§§]	Russia	2003–2005	8–9	Longitudinal cohort	424	Serum	∑Toxic Equiv. Quotient	↑	↓	↓	9	0	No
Flame retardants (Polybrominated diphenyl ethers, PBDE)	Small *et al.* (2009)[#]	USA	1973–1974	5–30	Longitudinal cohort	464	Serum	PBB	↑*		↑	10	1	No
	Harley *et al.* (2017)	USA	1999–2000	9	Longitudinal cohort	117	Serum	BDE-47	↔		↓*	10	0	No
								BDE-99	↑		↓*			
								BDE-100	↔		↓*			
								BDE-153	↓		↓*			
								∑PBDE	↔		↓*			
Parabens	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	MePB	↔		↓	10	0	No
								PrPB	↓		↔			
Phthalate diesters and their metabolites	Berger *et al.* (2018)	USA	1999–2000	9	Longitudinal cohort	537	Urine	MBzP	↓*		↓	8	0	No
								MCPP	↓*		↓*			
								cx-MiOP	↓*		↓*			
								cx-MiNP	↓*		↓			
								∑DEHPm**	↓		↓			
	Cathey *et al.* (2020)	Mexico	1997–2004	8–14	Longitudinal cohort	91	Urine	MEP	↑	↑	↑	8	1	No
								MiBP	↓	↓	↓			
								MnBP	↑	↑	↑*			
								MBzP	↑	↔	↑			
								MEHP	↑	↑	↑			
								5OH-MEHP	↑	↑	↑			
								5oxo-MEHP	↑	↑	↑			
								5cx-MEPP	↑	↑	↑			
								MCPP	↑	↑	↑			
								∑DEHPm**	↑	↑	↑			

Continued

Table III Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	GS	TV	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
	Ferguson *et al.* (2014)	Mexico	1994–2004	8–14	Longitudinal cohort	107	Urine	MEP	↓	↓	↑	7	1	Yes[(GS,TV,P)]
								MiBP	↑	↓	↑			
								MnBP	↑	↓	↑			
								MBzP	↑	↑	↑*			
								MEHP	↑	↓	↑			
								5OH-MEHP	↑	↓	↑			
								5oxo-MEHP	↑	↓	↑			
								5cx-MEPP	↑	↓	↑			
								MCPP	↑	↓	↑			
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	MEP	↓		↓	10	0	No
								MiBP	↓		↓			
								MnBP	↑		↓			
	Su *et al.* (2015)	Taiwan	2000–2001	8	Longitudinal cohort	59	Urine	MMP		↑		9	1	No
								MEP		↓				
								MnBP		↓				
								MBzP		↓				
								MEHP		↓				
								5OH-MEHP		↓				
								5oxo-MEHP		↓				
								∑DEHPm**		↓				
	Watkins *et al.* (2017a)	Mexico	1997–2004	8–14	Longitudinal cohort	109	Urine	MEP	↓	↓	↑	7	1	Yes[(GS,TV,P)]
								MBzP	↑	↑*	↑*			
								MCPP	↓	↓	↑			
								MiBP+MnBP	↑	↓	↑			
								∑DEHPm**	↑	↓	↑			
Polychlorinated biphenyl (PCB)	Grandjean *et al.* (2012)	Faroe Islands	1986–1987	14	Longitudinal cohort	438	Coord blood	∑PCB	↑	↑	↑	9	0	No
	Humblet *et al.* (2011)	Russia	2003–2005	8–9	Longitudinal cohort	424	Serum	∑PCB	↓*	↓	↓	9	0	No
Polychlorinated phenols/ organochloride pesticides	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	2,4-DCP	↓		↓	10	0	No
								2,5-DCP	↓		↓			
Polyfluoroalkyl chemicals/ per- and polyfluoroalkyl substances	Ernst *et al.* (2019)[#]	Denmark	1996–2002	11	Longitudinal cohort	565	Serum	PFOA	↓		↑	10	1	No
								PFOS	↓		↓			
Triclosan	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	155	Urine	TCS	↓		↓	10	0	No

Continued

Table III Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	GS	TV	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
Postnatal exposure														
Benzophenones and other UV filters	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	139	Urine	BP-3	↓		↓	10	0	No
	Huang *et al.* (2020)$_{(baseline)}$	China	2011	7–15	Cross-sectional	277	Urine	BP-2	↑	↓	↑	8	0	No
								BP-3	↑	↑	↑			
								EHMC	↑*	↑*	↑			
								4'-MAP	↑*	↑	↑			
								OD-PABA	↑	↓	↑			
	Huang *et al.* (2020)$_{(18\ months\ follow\text{-}up)}$		+18 months	+18 months		151		BP-2	↓	↓	↓			
								BP-3	↑	↑*	↑			
								EHMC	↑*	↑*	↓			
								4'-MAP	↓	↑	↓			
								OD-PABA	↓	↑	↓			
Bisphenol A	Ferguson *et al.* (2014)	Mexico	1994–2004	8–14	Longitudinal cohort	113	Urine	BPA	↑	↓	↓	7	1	No
	Kasper-Sonnenberg *et al.* (2017)[#]	Germany	2009–2010	8–10	Longitudinal cohort	250	Urine	BPA			↑	7	1	No
	Wang *et al.* (2017)	China	2011	9–18	Cross-sectional	671	Urine	BPA	↓	↓	↓	10	0	No
Dioxins	Burns *et al.* (2016)	Russia	2003–2005	8–9	Longitudinal cohort	473	Serum	$\sum_{Toxic\ Equiv.\ Quotient}$	↑*	↑*	↑	9	0	No
								$\sum_{Dioxin\ Like\ Compounds}$	↓	↑*	↓			
	Korrick *et al.* (2011)	Russia	2003–2005	8–9	Longitudinal cohort	453	Serum	TCDD	↓	↑*		9	0	No
								PCDD	↓	↑				
								PCDF	↑	↑				
Flame retardants (Polybrominated diphenyl ethers, PBDE)	Harley *et al.* (2017)	USA	1999–2000	9	Longitudinal cohort	266	Serum	BDE-47	↔		↑	10	0	No
								BDE-99	↔		↑			
								BDE-100	↓		↑			
								BDE-153	↓		↔			
								∑PBDE	↓		↑			
Parabens	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	139	Urine	MePB	↓		↑	10	0	No
								PrPB	↓*		↓			
Phthalate diesters and their metabolites	Ferguson *et al.* (2014)	Mexico	1994–2004	8–14	Longitudinal cohort	113	Urine	MEP	↓	↓	↓	7	1	Yes$^{(TV,\ P)}$
								MiBP	↑	↓	↑			
								MnBP	↓	↓*	↓			
								MBzP	↓	↓	↑			
								MEHP	↓	↓	↓			
								5OH-MEHP	↓	↑	↑			
								5oxo-MEHP	↓	↑	↑			
								5cx-MEPP	↑	↑	↑			
								MCPP	↓	↑	↓			

Continued

Table III Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	GS	TV	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
	Hou *et al.* (2015)[#]	Taiwan	2012–2013	7–15	Cross-sectional	270	Urine	MMP			↑*	9	I	No
								MEP			↑			
								MiBP			↓			
								MnBP			↑			
								MBzP			↑			
								MEHP			↑			
								5OH-MEHP			↑			
								5oxo-MEHP			↑			
								5cx-MEPP			↑			
								∑DEHPm**			↑			
								∑low-MWP			↑			
								∑high-MWP			↑			
								∑phthalates			↑			
	Kasper-Sonnenberg *et al.* (2017)[#]	Germany	2009–2010	8–10	Longitudinal cohort	250	Urine	MMP			↑	7	I	No
								MEP			↑			
								MiBP			↓			
								2OH-MiBP			↑			
								MnBP			↑			
								3OH-MnBP			↑			
								MBzP			↑			
								MEHP			↑*			
								5OH-MEHP			↑*			
								5oxo-MEHP			↑			
								5cx-MEPP			↑*			
								MiNP			↑			
								OH-MiNP			↑			
								oxo-MiNP			↑			
								cx-MiOP			↑			
								OH-MiDP			↑			
								oxo-MiDP			↑			
	Mouritsen *et al.* (2013)	Denmark	2006–2010	6–13	Longitudinal cohort	84	Urine	MEP		↑	↓	8	I	No
								MiBP+MnBP		↓	↓			
								MBzP		↓	↓			
								∑DEHPm**		↓	↓			
								∑DiNPm**		↓	↔			
								∑corr.phthalates		↓	↓			

Continued

Table III Continued

	Author, year	Location	Study period	Age at interview (years)	Study design	Sample size	Matrix	EDC	GS	TV	P	CR	Bias[§]	Main meta-analysis
									↓ Earlier ↑ Later ↔ None					
	Shi *et al.* (2015)	China	2010	7–14	Cross-sectional	172	Urine	MMP		↓	↑	10	1	No
								MEP		↓	↓			
								MnBP		↑*	↑			
								MEHP		↓	↑			
								5OH-MEHP		↑	↑*			
								5oxo-MEHP		↑	↑*			
								∑DEHPm**		↑	↑			
	Zhang *et al.* (2015) (baseline)	China	2011	7–14	Cross-sectional	252	Urine	MMP		↑	↑	10	0	Yes[(TV, P)]
								MEP		↓	↓			
								MnBP		↑	↑			
								MEHP		↓	↑			
								5OH-MEHP		↑	↑			
								5oxo-MEHP		↑	↑			
								∑DEHPm**		↑	↑			
	Zhang *et al.* (2015) (18 months follow-up)		+18 months	+18 months		222		MMP		↓	↑			
								MEP		↑	↓			
								MnBP		↓	↑			
								MEHP		↓	↓			
								5OH-MEHP		↓	↑			
								5oxo-MEHP		↓	↑			
								∑DEHPm**		↓	↑			
Polychlorinated biphenyl (PCB)	Burns *et al.* (2016)	Russia	2003–2005	8–9	Longitudinal cohort	473	Serum	∑non-dioxin-like PCB	↓	↓*	↓	9	0	No
	Den Hond *et al.* (2011)	Belgium	2003–2004	14–15	Cross-sectional	767	Serum	∑PCB	↓*		↓*	9	1	No
	Korrick *et al.* (2011)	Russia	2003–2005	8–9	Longitudinal cohort	453	Serum	∑PCB	↓	↑		9	0	No
Polychlorinated phenols/ organochloride pesticides	Den Hond *et al.* (2011)	Belgium	2003–2004	14–15	Cross-sectional	767	Serum	*p,p'*-DDE	↓*		↓*	9	1	No
								HCB	↓*		↓*			
	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	139	Urine	2,4-DCP	↓		↑	10	0	No
								2,5-DCP	↑		↑			
	Hou *et al.* (2015)[#]	Taiwan	2012–2013	7–15	Cross-sectional	270	Urine	Nonylphenol			↓	9	1	No
	Lam *et al.* (2014)	Russia	2003–2005	8–9	Longitudinal cohort	350	Serum	*p,p'*-DDE	↑	↑	↑	9	0	No
								HCB	↓	↑	↑			
								β-HCH	↑	↑	↓			
	Ye *et al.* (2017)[#]	China	2014–2015	9–16	Cross-sectional	463	Urine	3-PBA	↓	↓		8	1	No
Triclosan	Harley *et al.* (2019)	USA	1999–2000	9	Longitudinal cohort	139	Urine	TCS	↓		↑	10	0	No

[↑]Later onset; ↓Earlier onset; ↔ none detected
[#]Self-reported puberty outcome rather than clinical examination
[§]CR: Completeness of reporting ≥ 8 was considered sufficient; Bias: 1 = potential risk of bias, 0 = lower risk of bias
[§§]Measured postnatally in maternal biospecimen, but indicated as a proxy for prenatal exposure
[*]P-value <0.05
[(GS,TV,P)]Included in meta-analysis for genital stage [(GS)]; testicular volume [(TV)]; pubarche [(P)]
[**]Sums of selected phthalate metabolites and substitutes:
∑DEHPm: Molar sum of MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP and 2cx-MMHP expressed as DEHP
∑DiNPm: Molar sum of MiNP, OH-MiNP, oxo-MiNP and cx-MiOP expressed as DiNP
Low/high MWP: Low/high molecular weight phthalates
EDC, endocrine disrupting chemical.

et al., 2015; Burns et al., 2016; Namulanda et al., 2016, 2017; Harley et al., 2017, 2019; Kasper-Sonnenberg et al., 2017; Miao et al., 2017; Wang et al., 2017; Ye et al., 2017a,b; Berger et al., 2018; Binder et al., 2018; Attfield et al., 2019; Ernst et al., 2019; Cathey et al., 2020; Dobraca et al., 2020; Howland et al., 2020; Huang et al., 2020) that were based on 26 study populations reporting associations between prenatal and/or postnatal exposures to xenobiotic EDCs and timing of puberty outcomes for girls and boys: menarche (n = 31, self-report recall/self-report prospective diary: 30/1), thelarche (n = 25, clinical visual assessment/clinical assessment with breast palpitation/self-report: 1/18/6), pubarche in girls (n = 23, clinical assessment/self-report: 19/4), genital stage (n = 17, clinical assessment/self-report: 14/3), testicular volume (n = 15, orchidometer/self-report: 14/1) and pubarche in boys (n = 20, clinical assessment/self-report: 16/4). All 52 publications were used in the qualitative trend synthesis and 23 publications were eligible for meta-analysis.

Characteristics of the 52 publications in the systematic review are presented in Tables II and III. Overall, almost twice as many publications investigated puberty in girls (n = 41) compared with boys (n = 23), and most publications investigated more than one pubertal milestone as the outcome (n = 33). Assessment of associations according to postnatal EDC exposures (n = 36) was more prevalent compared with prenatal exposures to EDCs (n = 20) and only four publications assessed separate effects in both prenatal and postnatal exposure periods. Publications on prenatal exposure mainly assessed exposure during the second and/or third trimester (n = 9), while other publications collected samples prior to pregnancy (n = 4), in first trimester only (n = 1) or did not specify the time of collection within pregnancy (n = 3). Three publications collected maternal biospecimens after pregnancy: one at the time of delivery, one during breast feeding and one at the time of physical examinations of the child used as proxy for prenatal exposure. Publications on postnatal exposure mainly collected samples of biospecimen in the child prior to age 15 years (n = 25), but the overall age at exposure ranged from 5 to 19 years. In the majority of publications (n = 42), single spot biosamples were used to assess exposures in the study population, while in the remaining publications, biosamples were collected multiple times (up to six times) in a given period (data not shown). Of the 11 EDC compound groups investigated, most publications addressed exposure to phthalates (n = 19), polychlorinated phenols/pesticides (n = 18) and BPA (n = 12). The investigations predominantly used a longitudinal cohort design (60%) followed by a cross-sectional study design (35%), and most investigations were conducted on European (33%) and American (35%) study populations. Many individual publications were based on the same study populations, including The Breast Cancer and The Environment Research Program (BCERP) cohort (n = 7), Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) (n = 5), National Health and Nutrition Examination Survey (NHANES) (n = 4) and The Russian Children's Study (n = 4) (Supplementary Table SIV). Almost all included publications were published within the last 15 years (90%).

The completeness of reporting was generally high and only five publications were evaluated to have a low completeness of reporting. However, according to the predefined criteria, 50% of the included publications had a potential risk of bias primarily due to the potential for selection and information bias (Fig. 2).

Qualitative trend synthesis (n = 52 publications)

The qualitative trend synthesis provided data on 103 combinations of associations between prenatal or postnatal exposure to EDC compound groups and puberty outcomes. Selected trends (Tables II and III) by publication and Supplementary Table SIII by individual EDC in Supplementary data) are described below with a focus on the most investigated exposures and significant trends.

Menarche, thelarche and pubarche in girls

Three publications reported on prenatal exposure to BPA and ages at menarche, thelarche and pubarche, of which two were based on the same study population (Watkins et al., 2014, 2017b). These two publications indicated that exposure to BPA was associated with earlier thelarche and pubarche but later menarche, while the third publication with the largest study population (n = 537; Berger et al., 2018) consistently showed later onset for all three puberty outcomes (statistically significant for thelarche). Prenatal exposure to phthalates showed an overall trend toward earlier menarche, thelarche and pubarche, albeit the larger study by Berger et al. (2018) was an outlier and reported statistically significant associations with later onsets of puberty. Considering individual phthalate metabolites, prenatal exposure to MEP was consistently associated with earlier onset for all three outcomes. Prenatal exposure to polychlorinated phenols/pesticides showed a predominant trend toward earlier onset across all three puberty outcomes with several statistically significant associations for menarche.

Publications on postnatal exposure to BPA showed a relatively consistent trend toward later menarche and thelarche, but no clear trend for pubarche. Of the 12 publications on postnatal exposure to phthalates and pubertal timing in girls providing over 250 individual associations, no overall trend was observed with inconsistent directions of findings. Considering individual phthalate metabolites, postnatal exposure to MBzP, MEHP and $\sum$DEHPm seemed to support associations with earlier thelarche and later pubarche. Similarly, three publications on postnatal exposure to triclosan (Wolff et al., 2010, 2015; Harley et al., 2019) showed a clear trend toward earlier thelarche but tended toward later pubarche. Postnatal exposure to parabens showed a consistent trend toward earlier thelarche and pubarche, but less consistent findings for menarche. Postnatal exposure to polychlorinated phenols/pesticides did not show any clear trends for either menarche, thelarche or pubarche.

Genital stage, testicular volume and pubarche in boys

For puberty outcomes in boys, prenatal exposure to BPA showed a small trend toward earlier genital development, testicular enlargement and pubarche. Prenatal exposure to phthalates showed no trend for genital development and pubarche, but a predominant trend toward earlier onset was observed for testicular enlargement, although the most recent study by Cathey et al. (2020) indicated later onset.

Postnatal exposure to phthalates showed a weak trend toward later pubarche and earlier testicular enlargement, but only one publication investigated genital development, indicating earlier genital growth. Based on three publications, postnatal exposure to PCBs was associated with earlier onset across all puberty outcomes for boys. Publications on postnatal exposure to polychlorinated phenols/

pesticides showed a trend toward earlier onset of genital growth and pubarche, but no consistent trend for testicular enlargement.

Across all puberty outcomes in both girls and boys, prenatal exposures to UV filters and triclosan were based on a single study each and postnatal exposure to UV filters showed no clear overall trends. Exposures to dioxins and PAHs were generally investigated by too few studies to draw any overall conclusions.

Meta-analysis (n = 23 publications)

The meta-analysis of 23 publications enabled 18 summary risk estimates (prenatal/postnatal: 6/12) on pubertal onset in the main analysis (Strategy 1) following exposure to BPA, flame retardants, phthalates, polychlorinated phenols/pesticides, triclosan and UV filters. We observed varying heterogeneity in the estimates across all puberty outcomes and exposures (I^2 of 0–88%). Selected forest plots of the main analysis are included and presented in the manuscript in Figs 3 and 4, whereas the remaining forest plots are provided in Supplementary Figs S1 and S2.

Specific compound groups of EDCs (main analysis, Strategy 1)

Menarche. Twelve publications provided seven summary risk estimates for age at menarche following exposures to BPA, flame retardants, polychlorinated phenols/pesticides, phthalates, triclosan and UV filters. For prenatal exposures, only the summary estimate for prenatal exposure to phthalates was obtained and was close to unity (RR 1.01, 95% CI: 1.00–1.02; Fig. 3). Postnatal exposure to BPA showed a statistically non-significant association with later age at menarche (RR 0.95, 95% CI: 0.78–1.16) (Fig. 4A). But postnatal exposure to polychlorinated phenols/pesticides (Fig. 4B), flame retardants (Fig. 4C) and UV filters (Fig. 4D) was marginally associated with earlier age at menarche (RR 1.09, 95% CI: 0.99–1.19; RR 1.30, 95% CI: 0.94–1.79 and RR 1.04, 95% CI: 0.96–1.13, respectively). No associations were observed for postnatal exposure to phthalates (Fig. 4E) or triclosan (Fig. 4F), both with summary estimates of 1.00.

Thelarche. Seven publications provided three summary estimates for thelarche following exposures to BPA and phthalates. Prenatal exposure to phthalates showed no difference (RR 1.00, 95% CI: 0.99–1.01; Supplementary Fig. S1a). Postnatal exposure to BPA was associated with a statistically non-significant risk of later thelarche (RR 0.97, 95% CI: 0.87–1.09; Fig. 4G). No association was observed for postnatal exposure to phthalates and thelarche (RR 1.01, 95% CI: 1.00–1.02; Fig. 4H).

Pubarche in girls. Six publications provided three summary estimates for pubarche in girls following exposures to BPA, flame retardants and phthalates. No association was observed for prenatal exposure to phthalates and pubarche in girls (RR 1.01, 95% CI: 1.00–1.02) (Supplementary Fig. S1b). Postnatal exposures to BPA and phthalates were not associated with onset of pubarche (RR 1.01, 95% CI: 0.88–1.15 and RR 1.01, 95% CI: 1.00–1.02, respectively; Supplementary Fig. S2a and b).

Genital stage, testicular volume and pubarche in boys. Three publications provided five summary estimates for genital stage (n = 1), testicular volume (n = 2) and pubarche (n = 2) only following exposure to phthalates. The estimated meta-associations for boys were few and only based on a maximum of two different publications. Prenatal exposure to phthalates was associated with later genital development and pubarche onset (RR 0.98, 95% CI: 0.96–1.00 and RR 0.91, 95% CI: 0.84–0.98, respectively), but no association was observed for testicular enlargement (Supplementary Fig. S1c–e). Postnatal exposure to phthalates showed no association with testicular enlargement or pubarche in boys (Supplementary Fig. S2c and d).

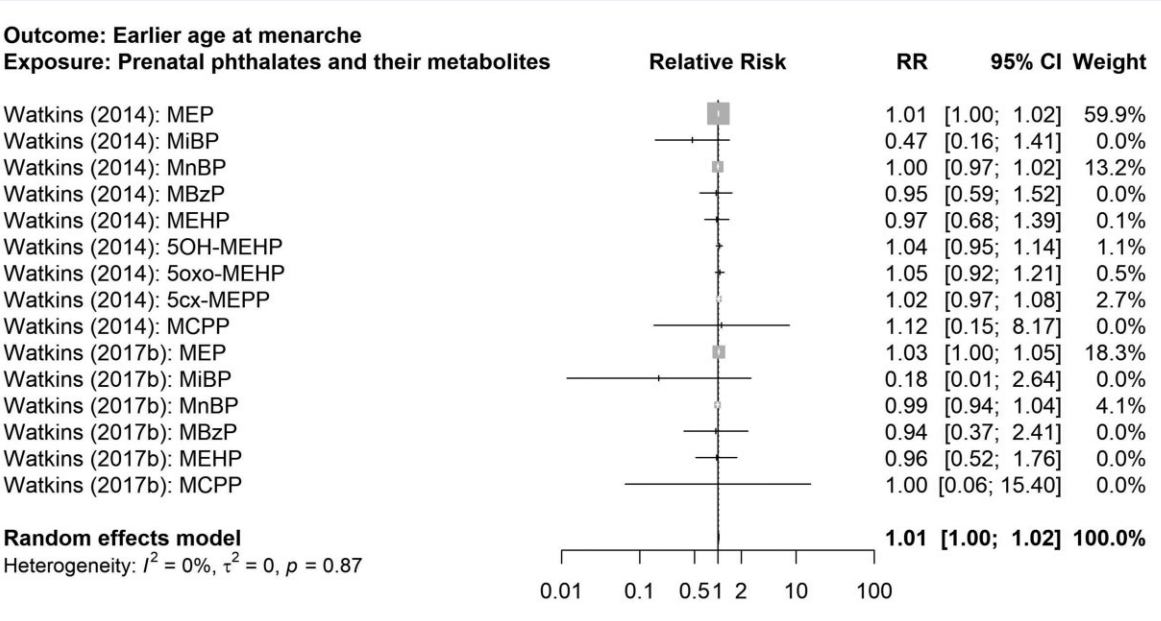

Figure 3. Summary estimates of the meta-analysis: associations between prenatal exposure to phthalates and their metabolites and menarche.

Persistent and non-persistent EDC compounds (Strategy 2)

Puberty outcomes in girls. Grouping EDCs into persistent and non-persistent compounds resulted in summary estimates for prenatal exposures that were based on relatively few publications. Prenatal exposures to non-persistent compounds were based on the same two publications by Watkins *et al.* (2014, 2017b) and showed essentially no association across all puberty outcomes in girls (Supplementary Fig. S1f–h). Prenatal exposure to persistent compounds was associated

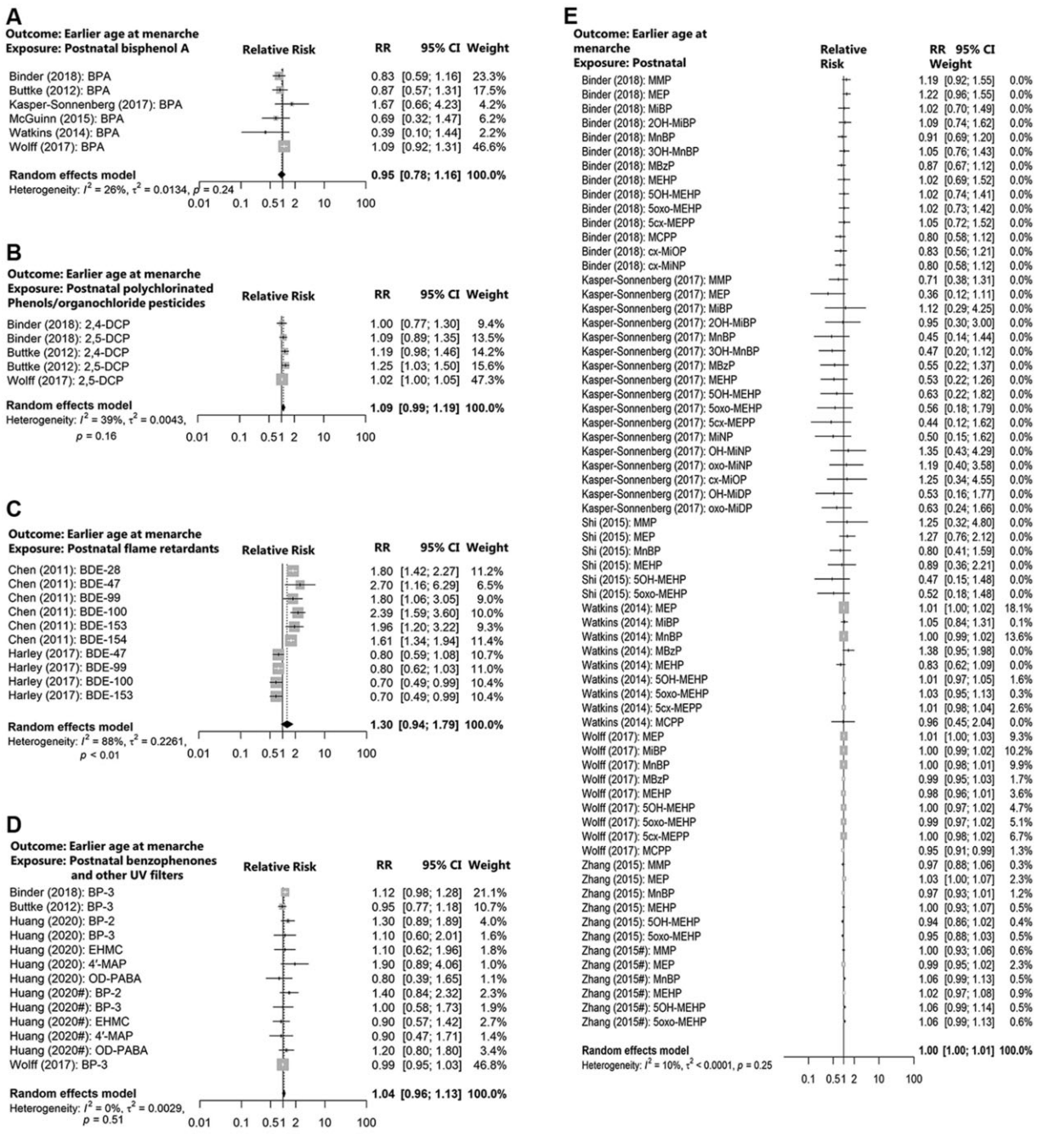

Figure 4. Summary estimates of the meta-analysis (Strategy 1): postnatal exposures and puberty outcomes in girls. (**A**) Associations between postnatal exposure to bisphenol A and menarche. (**B**) Associations between postnatal exposure to polychlorinated phenols and pesticides and menarche. (**C**) Associations between postnatal exposure to flame retardants and menarche. (**D**) Associations between postnatal exposure to benzophenones and other UV filters and menarche. (**E**) Associations between postnatal exposure to phthalates and their metabolites and menarche. (**F**) Associations between postnatal exposure to triclosan and menarche. (**G**) Associations between postnatal exposure to bisphenol A and thelarche. (**H**) associations between postnatal exposure to phthalates and their metabolites and thelarche.

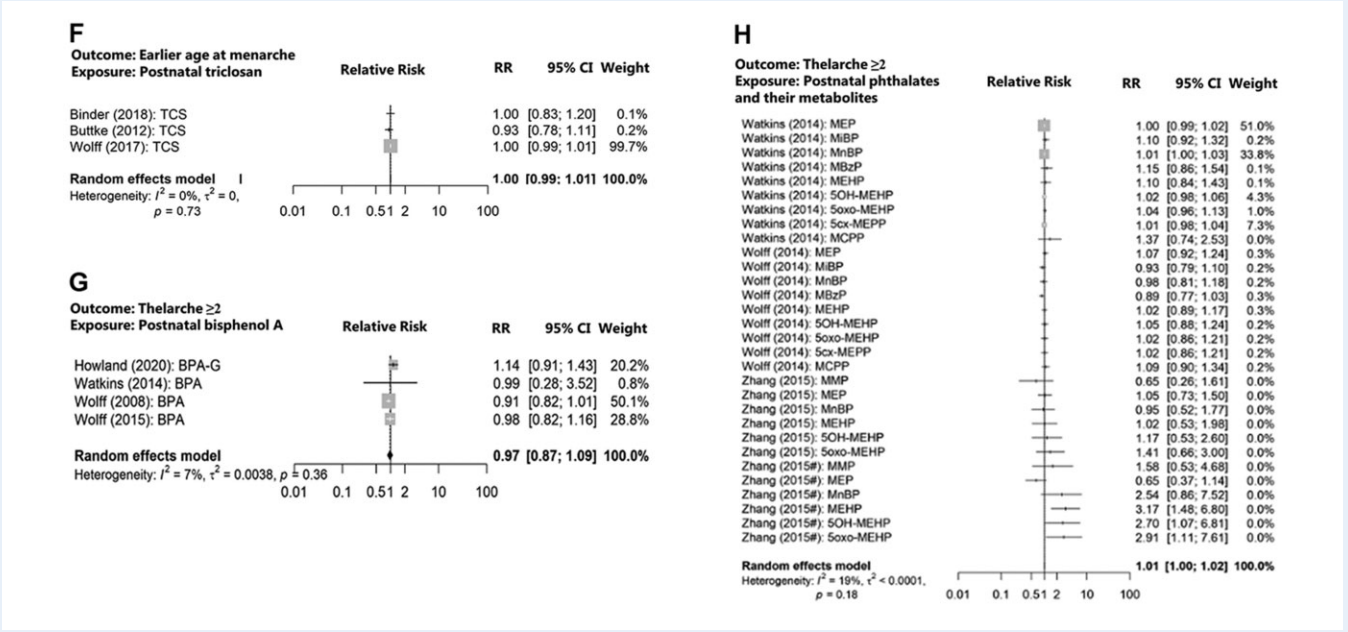

Figure 4. (Continued)

with later age at menarche (0.73, 95% CI: 0.63–0.84; Supplementary Fig. S1i).

Postnatal exposure to non-persistent compounds was associated with slightly earlier thelarche (RR 1.02, 95% CI: 0.99–1.05), but no difference for menarche and pubarche (RR 1.00, 95% CI: 1.00–1.01 and RR 1.01, 95% CI: 1.00–1.02) (Supplementary Fig. S2e–g). Postnatal exposure to persistent compounds showed statistically non-significant associations with earlier age at menarche (RR 1.09, 95% CI: 0.88–1.37) and later age at pubarche (RR 0.96, 95% CI: 0.80–1.14), but a significant association with later thelarche (odds ratio 0.73, 95% CI: 0.59–0.90) (Supplementary Fig. S2h–j).

Puberty outcomes in boys. Meta-associations for genital development, testicular enlargement and pubarche in boys following prenatal or postnatal exposures to non-persistent compounds were largely based on the same individual estimates as for exposure to phthalates and reflected the same subsequent summary estimates (Supplementary Fig. S1j–l and S2k–l). No summary estimates were enabled for exposures to persistent compounds.

Banned and suspicious EDC compounds (Strategy 3)

In the analysis of banned and suspicious exposure compounds, prenatal or postnatal exposures to EDCs were not associated with pubertal onset, with most of the non-statistically significant summary estimates ranging between RR 0.99 and 1.01 (data not shown).

Discussion

This systematic review pooled available evidence on the association between prenatal or postnatal exposures to xenobiotic EDCs and timing of pubertal onset in girls and boys. Although the findings of this review provide some evidence on the effect of exposure to EDCs on pubertal onset, the available data on specific exposure-outcome associations are limited and thus preclude strong concluding statements. The qualitative trend synthesis suggested that postnatal exposure to phthalates may be associated with an earlier thelarche and later pubarche. However, in the subsequent stringent meta-analysis, no clear overall association of EDCs on puberty development in girls and boys was evident across all outcomes. Based on current evidence, we were not able to identify pre- or postnatal windows of exposure as particularly critical and susceptible for effects of EDCs.

Overall findings of the review

Qualitative trend synthesis

Many of the identified trends in the qualitative trend synthesis of 52 publications were often subject to inconsistent findings within specific exposure-outcome associations and/or sometimes contradicting directions of findings across puberty outcomes for the same compound group. For a few specific exposure-outcome associations, the trend synthesis was able to provide an overall indication of an association, such as largely consistent trends toward later menarche and later thelarche following postnatal exposure to BPA. In the trend synthesis, we were also able to identify an association between postnatal exposure to phthalates (the compound group most investigated) and earlier thelarche but later pubarche, which could not be confirmed in the meta-analysis, potentially due to a lower number of included publications in our meta-analysis. These findings may also in part reflect different hormonal actions of thelarche (an estrogen-driven process) and pubarche (an androgen-driven process). However, the individual findings for prenatal exposure to phthalates indicated an overall direction toward earlier onset of all puberty outcomes in girls (menarche, thelarche, pubarche), although this trend was based on few publications and was relatively weak. For puberty in boys, the trend synthesis was not able

to identify any clear trends, probably as these were based on very few individual exposure-outcome associations. Despite some suggestive associations in the qualitative trend synthesis, many identified trends were not robust, and the overall effect of specific exposure compounds remained largely inconclusive.

Meta-analysis

The summary estimates from the meta-analysis of 23 publications provided scarce evidence on altered age of pubertal onset following prenatal or postnatal exposures to EDCs, largely due to difficulties in obtaining actual meta-associations based on sufficient data. Most exposure-outcome associations showed no overall effect, and summary risk estimates with indication of an association showed relatively small changes in pubertal onset with limited predictive power. On balance, the meta-associations provided less evidence for the included compounds with more individual associations, i.e. summary estimates on exposure to phthalates were based on most individual estimates but the resulting summary estimates generally indicated no associations. Applying different strategies did not provide additional perspectives on the overall findings. A few statistically significant associations for persistent compounds suggested later onset of puberty in girls, but given the many analyses performed, these individual associations may be a result of chance findings.

Quality, limitations and comparability of the included publications

The specific reporting quality of each of the 52 included publications was considered sufficiently high, though with a noteworthy potential risk of selection and information bias. In a broader sense, the overall research quality within the publication landscape was subject to several methodological challenges and inconsistencies. Most publications ascertained the respective puberty outcomes in a homogenous way using standardized clinical assessments, including visualization and palpation by trained clinicians, by standards of the Tanner staging of development. However, definitions of pubertal onset were surprisingly different and not all publications defined onset of puberty as having reached Tanner Stage 2. Regarding the use of self-reported data for age of menarche, some epidemiological publications prospectively followed and assessed menarche in children using a diary, whereas others solely relied on a one-time retrospective assessment with risk of recall bias and potential outcome misclassification. Standardized clinical definitions of pubertal onset across all puberty outcomes are therefore needed for future research to allow for formal comparison of evidence. Exposure assessments were relatively comparable across publications as we only included publications with reliable exposure biomarkers, but the specific levels of exposure were still assessed by different sample handling practices such as storage containers and storage time (historical cohorts), which may lead to EDC degradation or sample contamination. Importantly, timing of exposure assessment also varied significantly between publications and the specific exposure period may impact the association, a possible concern for *in utero* exposure during susceptible periods of fetal development or different windows throughout childhood. The predominant use of single spot biosamples during pregnancy and in childhood challenges interpretation of associations with full certainty and a risk of exposure misclassification is inevitable for non-persistent compounds, and potentially also for persistent compounds, especially depending on the specific chemical and source of exposure (diet, household products, cosmetics, etc.; Bloom *et al.*, 2007). Across all publications, there were generally important differences in methodological choices, especially regarding study design, sample size, statistical analyses, adjustment for creatinine, specific gravity and serum lipids and methods of log-transforming EDC exposure levels. Although most publications used a longitudinal cohort study design, a significant number of publications were cross-sectional despite the predictive limitations in assessing exposures at the same time as outcome with the risk of reverse causality. All these observed inconsistencies in methodological approaches may subsequently preclude any strong conclusions on the impact of EDCs on onset of puberty.

Critical windows of fetal development

Pregnancy is a critical period of development, during which the fetus is susceptible to harmful effects of exposures. Healthy fetal development largely depends on hormonal regulation and any disturbances of hormones could ultimately affect growth and development parameters. Therefore, we expected that prenatal exposures to EDCs might interfere with development of fetal endocrine systems and represent a critical window of exposure with regard to timing of pubertal onset. However, based on this review, we were unable to recognize prenatal exposures as particularly critical for effects of EDCs and evidence was too scarce to distinguish different windows of exposure during pregnancy.

Combined mixtures of EDC exposures

International biomonitoring data from the past four decades provide unequivocal documentation of human exposure to a mixture of xenobiotic substances, including persistent and non-persistent EDCs. There is increasing interest in ascertaining joint effects of chemicals, as chemical exposures rarely occur in isolation and the potential effects on pubertal perturbations likely depend on a mixture of exposures present in low concentrations rather than attributable to single EDC compounds. However, we were not able to evaluate the simultaneous exposures to different EDCs (the so-called cocktail effect; Kortenkamp, 2007, 2014), as all included publications considered one EDC compound at a time and we were unable to draw conclusions on the potentially additive or synergistic interactions between the investigated EDC compounds on the pubertal outcomes. In our meta-analyses, we attempted to address the combined joint effects within and between different classes of EDC compounds by pooling estimates according to various strategies (according to compound groups of EDCs, persistency and chemicals on the SVHC lists). We acknowledge that these analyses may be over-simplified, as the different EDCs vary in their biological modes of actions and potencies, but biological actions are not fully elucidated in the existing literature and ascertaining this with full certainty was beyond the scope of this systematic review.

Biological plausibility

Numerous studies have explored exposures to EDCs in relation to pubertal onset, but mostly focused on individual compounds and their association with timing of specific pubertal outcomes. In line with our findings from the trend synthesis, we previously reported that childhood excretion (biomarker of exposure due to correlation) of high levels of urinary phthalate metabolites was associated with a marked delay in the development of pubarche among girls (Frederiksen *et al.*, 2012). Similar findings were confirmed shortly hereafter in a US study (Wolff *et al.*, 2014), whereas others did not demonstrate an

association. A delay in pubarche may potentially be explained by the anti-androgenic properties of phthalates and result in later development of pubarche (Axelstad *et al.*, 2018). Despite a plausible biological mechanism, the varying anti-androgenic properties of individual phthalate metabolites were not accounted for in the respective study and the potential underlying mechanism remains largely speculative. Importantly, neither of these two mentioned studies reported their data in a way that allowed for their inclusion in our meta-analysis.

Strengths and limitations of the review

We have rigorously evaluated the evidence on prenatal and postnatal exposures using biomarkers to EDC compounds and pubertal onset in girls and boys. To our knowledge, this review includes all published studies in English (prior to 1 February 2021) fulfilling predefined criteria using a systematic and transparent search of the literature. Unlike previous systematic reviews, we included both a qualitative trend synthesis and a meta-analysis with summary risk estimates applying different approaches for exposure groupings.

However, an important limitation of our systematic review is the rather limited number of available studies for investigating specific exposure (by compound)-outcome associations and some of the summary risk estimates in the meta-analysis lack sufficient data to allow for reliable meta-associations. Given the limited data, we were compelled to investigate exposure in childhood under two broadly defined exposure categories, within fetal life and during childhood (after birth). We were not able to investigate finer windows of exposure for which there may be differences in susceptibility and effects of exposure, e.g. early childhood versus pre-puberty. Another inherent limitation is the methodological heterogeneity among studies in study design, statistical analyses, definitions of puberty etc. that resulted in a substantial but necessary exclusion of publications in the meta-analysis to enable comparison of individual estimates. Even though these limitations in comparing studies were unavoidable, interpretation of the meta-associations on the impact of EDCs should be made with caution.

As previously discussed, our review is also limited by only assessing individual effects of EDC compounds and therefore not including possible synergies and mixture effects, even though a combined exposure to multiple EDCs may in fact represent the underlying explanation to any observed association between EDCs and timing of pubertal onset.

Conclusions and wider implications

In this large systematic review with a stringent meta-analysis, we did not find consistent evidence for associations between prenatal or postnatal exposures to xenobiotic EDCs and changes in pubertal timing in girls and boys. According to statistically significant associations in the qualitative trend synthesis, postnatal exposure to phthalates may be associated with earlier thelarche and later pubarche, consistent with their anti-androgenic properties. Only a few specific exposure-outcome associations were identified in the meta-analysis but with limited predictive power. We were not able to identify specific pre- or postnatal windows of exposure as particularly critical and susceptible for effects of EDCs. Current evidence is subject to several methodological challenges and inconsistencies and the evidence on specific exposure-outcome associations remains too scarce to firmly confirm EDC exposure as a risk factor for change in age of pubertal onset. Adding to the complexity of this research field, virtually all children are exposed to a multitude of varying EDCs throughout their fetal and postnatal lifetime and these exposures often correlate, which makes identifying individual EDC contributions to altered timing of pubertal onset difficult to ascertain. To create a more uniform foundation for future comparison of evidence and to strengthen pooled studies, we recommend the use of more standardized approaches in the choice of statistical analyses, with transformation of non-normal distributed EDC exposures, and in the definitions and assessments of puberty outcomes. The impact of mixtures of EDC exposures on the association also remains unestablished and would be valuable to elucidate for prenatal and postnatal windows of exposure. Future large, longitudinal epidemiological studies are needed to clarify the impact of EDCs on pubertal timing, as some EDC exposures are increasing and have potential health implications for young children.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

All data are incorporated into the article and its online supplementary data.

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Authors' roles

A.J. and E.V.B. designed the concept of the study and supervised the study. T.K. performed the systematic literature search and screening of publications with support from E.V.B. T.K. and C.S.O. evaluated the quality of the included studies. T.K. and C.S.U. drafted the tables with support from E.V.B., while L.S.G. validated the content of the final table versions. C.S.U. and T.K. performed the qualitative analyses with support from L.S.G. and E.V.B. Y.H.L. performed the statistical analyses. A.M.A. and H.F. provided EDC expertise and strategies for grouping exposure compounds. B.A.C. provided guidance on statistical methods and R.H. provided expertise in relation to pubertal onset. C.S.U. drafted the manuscript with support from T.K. and E.V.B. All authors contributed to manuscript revisions and the final draft of the manuscript.

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Conflict of interest

None declared.

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